Heiko Brennenstuhl, MD, MBA

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Institute of Human Genetics
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SUMMARY

Dr. Heiko Brennenstuhl is a board-certified pediatrician and junior research group leader at the Institute of Human Genetics at the University Hospital Heidelberg in Germany. Specializing in genomic newborn screening, Heiko is driven by a profound passion for improving neonatal and pediatric healthcare and leads research initiatives aimed at identifying genetic disorders in infants at the earliest stages of life. Heiko earned his medical degree from the University of Tübingen with extensive clinical rotations in Germany, the USA, the U.K., China, and Switzerland. Alongside his medical qualifications, Heiko holds an MBA in Health Management from the University of Applied Sciences Neu-Ulm, reflecting his commitment to effective healthcare administration and strategic leadership.

EDUCATION

Board-Certified Pediatrician, Ärztekammer Baden-Württemberg — April 2023

Master of Business Administration, Management and Leadership in Health Care — July 2021
University of Applied Sciences, Neu-Ulm, Germany
Thesis title: *"Development of recommendations for the implementation and quality assurance of an innovative gene therapy approach as well as derivation of a cost calculation for an outpatient follow-up model"*
Degree: *1.7*

Medical Degree, Eberhard Karls Universität Tübingen, Germany — July 2016
Doctoral thesis work performed at the Hertie Institute for Clinical Brain Research, Department for General Neurology, Laboratory for Molecular Neuro-Oncology
Thesis title: *"IκBζ, an atypical inhibitor of NFκB-mediated cell death in glioblastoma"*
Degree: *Magna cum laude*

PROFESSIONAL EXPERIENCE

Institute of Human Genetics, University Heidelberg, Germany — Since May 2022
Medical Doctor and Junior Research Group Leader
- Genome Sequencing Pilot Study to evaluate feasibility and scalibility for genomic newborn screening
- Clinical care and consulting of patients with suspected genetic disorders

Center for Child and Adolescent Medicine, Heidelberg, Germany — October 2016 - May 2022
Medical Doctor at the Department of General Pediatrics, Metabolism, Gastroenterology, Nephrology
- Clinical care of children and adolescents with congenital and acquired diseases in the field of neurometabolism, pediatric infectious diseases, autoimmune diseases and childhood cancers
- Research on genotype-phenotype correlations for rare neurometabolic disorders

Dietmar-Hopp Metabolic Center, Heidelberg, Germany — October 2018 - May 2022
Post-doctoral researcher at the group of inborn errors of neurotransmitters and pterins
- Exploring congenital disorders of neurotransmission with induced pluripotent stem cells to generate cerebral organoids.

FUNDING / GRANTS (Competitively acquired third-party funds)

- Fritz Thyssen Foundation Conference Funding: "Towards Genomic Newborn Screening in Germany: Opportunities, Risks, and Challenges", sum 17.640 €
- Klinz Foundation project funding: "Human stem cell-based cerebral organoids for research of diagnostics and therapy of succinate-semialdehyde dehydrogenase deficiency", sum 20.000 €
- APS project funding: "Investigation of the pathophysiology of primary neurotransmitter defects using induced pluripotent stem cells (iPS) and iPS-based cerebral organoids", sum 10.000 €
- Innovation award for outstanding SSADH research, SSADH Defizit e.V., sum 1.000 €
- Physician Scientist Scholarship, Medical Faculty University Heidelberg
- Project funding, SSADH Defizit e.V., structured course in organoid generation at LMU Munich, sum 3.000 €
- Project funding, SSADH Defizit e.V., "Immunohistochemical characterization of SSADH organoids", sum 5.000 €
- DAAD scholarship to study at Warren Alpert Medical School, Brown University, Providence, Rhode Island, USA
- IZKF scholarship, Medical Faculty University Tübingen, sum 13.500 € (divided to 6.000 € personal budget and 7.500 € consumables)

PUBLICATIONS (First / Co-First or Last Author)

- Betzler, I. R., Hempel, M., Mütze, U., Kölker, S., Winkler, E., Dikow, N., Garbade, S. F., Schaaf, C. P., **Brennenstuhl, H.**. (2024). Comparative analysis of gene and disease selection in genomic newborn screening studies. Journal of inherited metabolic disease, https://doi.org/10.1002/jimd.12750
- **Brennenstuhl, H.**, Schaaf, C. P. (2023). Genomisches Neugeborenenscreening - Forschungsansätze, Herausforderungen und Chancen. Bundesgesundheitsbl. https://doi.org/10.1007/s00103-023-03777-2
- Christmann, M., Opladen, T., **Brennenstuhl, H.** (2023). Sprachliche Auffälligkeiten bei Succinat-Semialdehyd-Dehydrogenase-Mangel – die Untersuchung der Sprache bei drei von SSADHD betroffenen Personen. Praxis Sprache 2023.
- Schröter, J., Dattner, T., Hüllein, J., Jayme, A., Heuveline, V., Hoffmann, G. F., Kölker, S., Lenz, D., Opladen, T., Popp, B., Schaaf, C. P., Staufner, C., Syrbe, S., Uhrig, S., Hübschmann, D., **Brennenstuhl, H.** (2022). aRgus: Multilevel visualization of non-synonymous single nucleotide variants & advanced pathogenicity score modeling for genetic vulnerability assessment. (2023). Computational and Structural Biotechnology Journal. https://doi.org/10.1016/j.csbj.2023.01.027
- Keller, M., **Brennenstuhl, H.**, Kuseyri Hubschmann, O., Manti, F., Julia Palacios, N. A., Friedman, J., Yildiz, Y., Koht, J. A., Wong, S. N., Zafeiriou, D. I., Lopez-Laso, E., Pons, R., Kulhanek, J., Jeltsch, K., Serrano-Lomelin, J., Garbade, S. F., Opladen, T., Goez, H., International Working Group on Neurotransmitter related, Disorders (2021). Assessment of intellectual impairment, health-related quality of life, and behavioral phenotype in patients with neurotransmitter related disorders: Data from the iNTD registry. J Inherit Metab Dis, 44(6), 1489-1502.
- **Brennenstuhl, H.**, Nashawi, M., Schroter, J., Baronio, F., Beedgen, L., Gleich, F., Jeltsch, K., von Landenberg, C., Martini, S., Simon, A., Thiel, C., Tsiakas, K., Opladen, T., Kolker, S., Hoffmann, G. F., Haas, D., Unified Registry for Inherited Metabolic Disorders, C., and the European Registry for Hereditary Metabolic, D. (2021). Phenotypic diversity, disease progression, and pathogenicity of *MVK* missense variants in mevalonic aciduria. J Inherit Metab Dis, 44(5), 1272-1287.
- **Brennenstuhl, H.**, Christ, S., Kock, V. (2021). The "Young Metabolic Society": An interest group for young professionals in the field of metabolic medicine. J Inherit Metab Dis, 44(4), 789.
- **Brennenstuhl, H.**, Will, M., Ries, E., Mechler, K., Garbade, S., Ries, M. (2021). Patterns of extreme temperature-related catastrophic events in Europe including the Russian Federation: a cross-sectional analysis of the Emergency Events Database. BMJ Open, 11(6), e046359.
- **Brennenstuhl, H.**, Opladen, T. (2021). Neue biochemische Methoden zur Diagnose des Aromatischen L-Amino-säure Decarboxylase (AADC)-Mangels. Neuropädiatrie in Klinik und Praxis, 20. Jg.
- **Brennenstuhl, H.**, Didiasova, M., Assmann, B., et al. Succinic Semialdehyde Dehydrogenase Deficiency: in vitro and in silico characterization of a novel pathogenic missense variant and analysis of the mutational spectrum of *ALDH5A1*. Int. J. Mol. Sci., 2020, 21(22), 8578.
- **Brennenstuhl, H.**, Garbade, S.F., Okun, J.G., et al. Semi-quantitative detection of a vanillactic acid / vanillylmandelic acid ratio in urine is a reliable diagnostic marker for aromatic L-amino acid decarboxylase deficiency. Mol Genet Metab. 2020; 1096-7192(20)30151-7.

- **Brennenstuhl, H.**, Kohlmuller, D., Gramer, G., et al. High throughput newborn screening for aromatic L-amino-acid decarboxylase deficiency by analysis of concentrations of 3-O-methyldopa from dried blood spots. J Inherit Metab Dis. 2020;43(3):602-610.
- **Brennenstuhl, H.**, Jung-Klawitter, S., Assmann, B., Opladen, T.. Inherited Disorders of Neurotransmitters: Classification and Practical Approaches for Diagnosis and Treatment. Neuropediatrics. 2019;50(1):2-14.
- **Brennenstuhl, H.**, Armento, A., Braczysnki, A.K., Mittelbronn, M., Naumann, U. (2015). IκBζ, an atypical member of the inhibitor of NFκB family, is induced by gamma-irradiation in glioma cells, regulating cytokine secretion and associated with poor prognosis. Int J Oncol. 2015;47(5):1971-1980.

PUBLICATIONS (Co-Authorships)

- Doll, E. S., Lerch, S. P., Schmalenberger, K. M., Alex, K., Kölker, S., **Brennenstuhl, H.**, Pereira, S., Smith, H., Winkler, E. C., Mahal, J., Ditzen, B. (2025). How do parents decide on genetic testing in pediatrics? A systematic review. Genetics in medicine : official journal of the American College of Medical Genetics, 101390. Advance online publication. https://doi.org/10.1016/j.gim.2025.101390
- Valentin, I., Caro Martin, M. D. P., Fischer, C., **Brennenstuhl, H.**, Schaaf, C. P. (2025). The Natural Course of Bosch-Boonstra-Schaaf Optic Atrophy Syndrome. Clinical genetics, 10.1111/cge.14731. Advance online publication. https://doi.org/10.1111/cge.14731
- Schnabel-Besson, E., Mütze, U., Dikow, N., Hörster, F., Morath, M. A., Alex, K., **Brennenstuhl, H.**, Settegast, S., Okun, J. G., Schaaf, C. P., Winkler, E. C., Kölker, S. (2024). Wilson and Jungner Revisited: Are Screening Criteria Fit for the 21st Century?. International journal of neonatal screening, 10(3), 62. https://doi.org/10.3390/ijns10030062
- Julia-Palacios, N., Kuseyri Hübschmann, O., Olivella, M., Pons, R., Horvath, G., Lücke, T., Fung, CW., Wong, SN., Cortès-Saladelafont, E., Rovira-Remisa, MM., Yıldız, Y., Mercimek-Andrews, S., Assmann, B., Stevanović, G., Manti, F.,**Brennenstuhl, H.**, Jung-Klawitter, S., Jeltsch, K., Sivri, HS., Garbade, SF., García-Cazorla, À., Opladen, T. (2024). The continuously evolving phenotype of succinic semialdehyde dehydrogenase deficiency. J Inherit Metab Dis. 2024 Mar 18. doi: 10.1002/jimd.12723.
- Frank, S., Gabassi, E., Käseberg, S., Bertin, M., Zografidou, L., Pfeiffer, D., **Brennenstuhl, H.**, Falk, S., Karow, M., Schweiger, S (2024). Absence of the RING domain in MID1 results in patterning defects in the developing human brain. Life Sci Alliance. 2024 Jan 18;7(4):e202302288. https://doi.org/10.26508/lsa.202302288.
- Wimmer, M. C., **Brennenstuhl, H.**, Hirsch, S., Dötsch, L., Unser, S., Caro, P., Schaaf, C. P. (2024). Hao-Fountain syndrome: 32 novel patients reveal new insights into the clinical spectrum. Clin Genet. 2024 Jan 14. https://doi.org/10.1111/cge.14480
- Maaß, G.F., **Brennenstuhl, H.**, Schaaf, C.P. (2023). Morbidity and mortality in Schaaf-Yang syndrome. Annals of Translational Medicine, https://dx.doi.org/10.21037/atm-23-1718
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- Roubertie, A., Opladen, T., **Brennenstuhl, H.**, Hübschmann, O. K., Flint, L., Willemsen, M. A., Leuzzi, V., Cazorla, A. G., Kurian, M. A., François-Heude, M. C., Hwu, P., Ben Zeev, B., Kiening, K., Roujeau, T., Pons, R., Pearson, T. S. (2023). Gene therapy for aromatic L-amino acid decarboxylase deficiency: requirements for safe application and knowledge-generating follow-up. Journal of inherited metabolic disease, 10.1002/jimd.12649. https://doi.org/10.1002/jimd.12649
- Käseberg, S., Bertin, M., Menon, R., Gabassi, E., Todorov, H., Frank, S., **Brennenstuhl, H.**, Lohrer, B., Winter, J., Krummeich, J., Winkler, J., Winner, B., Weis, E., Hartwich, D., Diederich, S., Luck, K., Gerber, S., Lunt, P., Berninger, B., Falk, S., Schweiger, S., Karow, M. (2023). Dynamic X-chromosomal reactivation enhances female brain resilience. bioRxiv 2023.06.17.545424; doi: https://doi.org/10.1101/2023.06.17.545424
- Vogel, G. F., Mozer-Glassberg, Y., Landau, Y. E., Schlieben, L. D., Prokisch, H., Feichtinger, R. G., Mayr, J. A., **Brennenstuhl, H.**, Schröter, J., Pechlaner, A., Alkuraya, F. S., Baker, J. J., Barcia, G., Baric, I., Braverman, N., Burnyte, B., Christodoulou, J., Ciara, E., Coman, D., Das,

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- Goetz, M., Schröter J., Dattner , T., **Brennenstuhl, H.**, Lenz, D., Opladen, T., Hörster, F., Okun, J. G., Hoffmann, G. F., Kölker, S., Staufner, C. (2022). Genotypic and phenotypic spectrum of cytosolic phosphoenolpyruvate carboxykinase deficiency. Molecular Genetics and Metabolism. Volume 137, Issues 1–2, September–October 2022, Pages 18-25. https://doi.org/10.1016/j.ymgme.2022.07.007
- Scharping, M., **Brennenstuhl, H.**, Garbade, S.F., Wild, B., Posset, R., Zielonka, M., Kölker, S., Haun, M.W., Opladen, T. Unmet Needs of Parents of Children with Urea Cycle Disorders. Children 2022, 9, 712. https://doi.org/10.3390/children9050712
- Schröter, J., Popp, B., **Brennenstuhl, H.**, Döring, J. H., Donze, S. H., Bijlsma, E. K., van Haeringen, A., Huhle, D., Jestaedt, L., Merkenschlager, A., Arelin, M., Gräfe, D., Neuser, S., Oates, S., Pal, D. K., Parker, M. J., Lemke, J. R., Hoffmann, G. F., Kölker, S., Harting, I., Syrbe, S. (2022). Complementing the phenotypical spectrum of *TUBA1A* tubulinopathy and its role in early-onset epilepsies. European journal of human genetics : EJHG, 10.1038/s41431-021-01027-0. Advance online publication. https://doi.org/10.1038/s41431-021-01027-0
- Weiß, C., Ziegler, A., Becker, L. L., Johannsen, J., **Brennenstuhl, H.**, Schreiber, G., Flotats-Bastardas, M., Stoltenburg, C., Hartmann, H., Illsinger, S., Denecke, J., Pechmann, A., Müller-Felber, W., Vill, K., Blaschek, A., Smitka, M., Stam, L. v. d., Weiss, K., Winter, B., Goldhahn, K., Plecko, B., Horber, V., Bernert, G., Husain, R. A., Rauscher, C., Trollmann, R., Garbade, S. F., Hahn, A., v.d. Hagen, M.,Kaindl, A. M. (2021). Gene replacement therapy with onasemnogene abeparvovec in children with spinal muscular atrophy aged 24 months or younger and bodyweight up to 15 kg: an observational cohort study. Lancet Child Adolesc Health. 2021 Oct 28:S2352-4642(21)00287-X.
- Opladen, T., **Brennenstuhl, H.**, Kuseyri Hübschmann, O., Call, D., Green, K., Schara, U., Rascher, W., Hövel, A., Assmann, B., Kölker, S., Westhoff, J. H., Walter, M., Ziegler, A., Hoffmann, G. F., Kiening, K. (2021). Die intrazerebrale Gentherapie des Aromatischen-L-Aminosäure-Decarboxylase-Mangels mit Eladocagene exuparvovec. Monatsschrift Kinderheilkunde, 169(8), 738-747.
- Longo, C., Montioli, R., Bisello, G., Palazzi, L., Mastrangelo, M., **Brennenstuhl, H.**, de Laureto, P. P., Opladen, T., Leuzzi, V., Bertoldi, M. (2021). Compound heterozygosis in AADC deficiency: A complex phenotype dissected through comparison among heterodimeric and homodimeric AADC proteins. Mol Genet Metab, 134(1-2), 147-155.
- Semino, F., Schroter, J., Willemsen, M. H., Bast, T., Biskup, S., Beck-Woedl, S., **Brennenstuhl, H.**, Schaaf, C. P., Kolker, S., Hoffmann, G. F., Haack, T. B., Syrbe, S. (2021). Further evidence for de novo variants in SYNCRIP as the cause of a neurodevelopmental disorder. Hum Mutat, 42(9), 1094-1100.
- Döring, J. H., Schröter, J., Jüngling, J., Biskup, S., Klotz, K. A., Bast, T., Dietel, T., Korenke, G. C., Christoph, S., **Brennenstuhl, H.**, Rubboli, G., Møller, R. S., Lesca, G., Chaix, Y., Kölker, S., Hoffmann, G. F., Lemke, J. R., Syrbe, S. (2021). Refining Genotypes and Phenotypes in KCNA2-Related Neurological Disorders. International Journal of Molecular Sciences, 22(6).
- Lenz, D., Stahl, M., Seidl, E., **Brennenstuhl, H.**, et al. Rescue of respiratory failure in pulmonary alveolar proteinosis due to pathogenic MARS1 variants. Pediatric Pulmonology. 2020;55:3057–3066.
- Lenz, D., Smith, D.E.C., Crushell, E., ..., **Brennenstuhl, H.**, et al. Genotypic diversity and phenotypic spectrum of infantile liver failure syndrome type 1 due to variants in LARS1. Genetics in Medicine. 22, 1863–1873 (2020)
- Didiasova, M., Banning, A., **Brennenstuhl, H.**, et al. Succinic Semialdehyde Dehydrogenase Deficiency: An Update. Cells. 2020;9(2).
- Schotterl, S., **Brennenstuhl, H.**, Naumann, U. Modulation of immune responses by histone deacetylase inhibitors. Crit Rev Oncog. 2015;20(1-2):139-154.

PUBLICATIONS (ABSTRACTS)

- Schröter, J., Dattner, T., Hüllein, J., Jayme, A., Heuveline, V., Hoffmann, G. F., Kölker, S., Lenz, D., Opladen, T., Popp, B., Schaaf, C. P., Staufner, C., Syrbe, S., Uhrig, S., Hübschmann, D., **Brennenstuhl, H.** (2022). aRgus: a versatile tool for variant visualization and advanced prediction score modeling in inherited metabolic diseases. Abstracts 2022: 35th Annual Symposium Arbeitsgemeinschaft Pädiatrische Stoffwechselstörungen (APS; Society for Pediatric Metabolic Medicine). Monatsschr Kinderheilkd (2022). https://doi.org/10.1007/s00112-022-01624-3
- Juliá-Palacios, N., Kuseyri Hübschmann, O., Olivella, M., Pons, R., Horvath, G., Lücke, T., Fung, C.W., Cortès-Saladelafont, E., Yildiz, Y., Mercimek-Andrews, S., Assmann, B., Stevanovic, G., Manti, F., **Brennenstuhl, H.**, Jung-Klawitter, S., Jeltsch, K., Sivri, S., Garbade, S. F., García-Cazorla, A.,

Opladen, T. Succinic Semialdehyde Dehydrogenase deficiency: Expanding the phenotypic and genotypic spectrum. J Inherit Metab Dis. Vol 45, Issue S1, 0141-8955, https://doi.org/10.1002/jimd.12536.

- Weiß, C., Ziegler, A., Becker, L. L., Johannsen, J., **Brennenstuhl, H.**, Schreiber, G., Flotats-Bastardas, M., Stoltenburg, C., Hartmann, H., Illsinger, S., Denecke, J., Pechmann, A., Müller-Felber, W., Vill, K., Blaschek, A., Smitka, M., Stam, L. v. d., Weiss, K., Winter, B., Goldhahn, K., Plecko, B., Horber, V., Bernert, G., Husain, R. A., Rauscher, C., Trollmann, R., Garbade, S. F., Hahn, A., v.d. Hagen, M.,Kaindl, A. M. (2021). Real-World Data for Onasemnogen Abeparvovec (Zolgensma) in Spinal Muscular Atrophy. Neuropediatrics, 52(S 01), FV5.09.
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- Eckhardt, I., Merbecks, M. B., Jacobi, S. F., Lechner, C., Becker, L. L., Balks, M. F., Scala, M., Kampmann, K., Ortner, G. R., Schmid, F., Hensel, K. O., Pokora, R., Eichinger, M., Drossard, S., **Brennenstuhl, H.**, Christ, S., Kock, V., Krey, I., Meyer, R., Schulz, J., Ferger,M. D., Nissen, G., Happle, C. Kohlfürst, D.S., Jakob, J. (2021). "Gemeinsam stark – für eine bessere Kinder- und Jugendmedizin!". Monatsschrift Kinderheilkunde, 169(11), 1083-1087.
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- **Brennenstuhl, H.**, Kohlmuller, D., Gramer, G., et al. The quantification of 3-O-methyldopa in dried blood spots enables high-throughput newborn screening for aromatic L-amino-acid decarboxylase deficiency. Monatsschrift Kinderheilkunde. 168:277–290, 2020.
- **Brennenstuhl, H.**, Opladen, T., Ebrahimi-Fakhari, D., et al. Induced pluripotent stem cells (iPSCs) and iPSC-derived cerebral organoids as a tool to model Succinic Semialdehyde Dehydrogenase Deficiency. J Inherit Metab Dis. Vol 42, Issue S1.
- **Brennenstuhl, H.**, Opladen, T., Ebrahimi-Fakhari, D., et al. The use of patient-derived induced pluripotent stem cells (iPSCs) and iPSC-derived cerebral organoids to explore pathomechanisms of succinc semialdehyde dehydrogenase deficiency. Monatsschrift Kinderheilkunde. 167:365, 2019.

MEMBERSHIPS

- Founding member and current chairman of the Young Metabolician Society within the Association for Pediatric Metabolic (APS) to improve educational opportunities and resources for young professionals in the field of inherited metabolic disorders
- Member of the German Society of Human Genetics (GfH)
- Member of the Association for Pediatric Metabolic (APS)
- Member of the German Society of Pediatrics and Adolescent Medicine (DGKJ)

Neckargemünd, February 25, 2025